

REMARKS

Applicant has amended the specification to delete reference to Tables I-IV.

Applicant appreciates that the Examiner has withdrawn the earlier rejection of the application on grounds of "inherency." The present application was, however, rejected by the Examiner, not on grounds of anticipation or unobviousness (prior art) but, rather, on the ground of 35 U.S.C. § 101, non-statutory subject matter, lack of utility. Applicant respectfully disagrees with the Examiner's conclusion.

The present invention, as claimed, is a significant and patentable advance over the prior art and is extremely useful. Specifically, the composition of matter, as claimed, is the composition used for molecular weight determinations at a high degree of accuracy for large molecular weight compounds. Prior to the present invention, mass spectrometers having nominal mass ranges far below the molecular weight of the compound sought to be determined could not be accurately "measured." By use of the present invention, the claimed composition of matter, relatively low nominal mass range spectrometers can provide accurate determinations of molecular weight of large molecular weight compounds. This is extremely useful in the pharmaceutical and bio-engineering fields, among many others.

The Examiner rejected the application on the ground of lack of utility because he felt that the claimed composition of matter was merely "an intermediate product to make other compounds, without regard for the usefulness of latter compounds." This is not accurate. The present invention, as claimed, is a composition of matter which is the end product itself. It is not an intermediate product. Rather, the claimed composition of matter, highly multiply charged ions, are analyzed in a mass spectrometer and, as a consequence of the multiple charges on the claimed ions, molecular weight determinations of large compounds are determined in mass spectrometers having nominal mass ranges below the molecular weight of the compound under review.

The cases relied on by the Examiner, In re Joly, 153 U.S.P.Q. 45 and In re Kirk, 153 U.S.P.Q. 49 are not analogous to the present invention. More specifically, in the Joly case, the CCPA affirmed the rejection of the Patent Office of a claimed chemical compound because the claimed compound was merely an intermediate compound useful in making additional compounds and, yet, neither the intermediate compound nor the end-result

compound were described in the specification as having any utility. The CCPA indicated that the mere disclosure that the claimed chemical compound may be used as an intermediate to make other compounds without regard to the usefulness of the latter compounds was not an adequate teaching of utility. Applicants do not disagree with this statement of law. It is, however, not appropriately applied to the claimed invention. The Examiner is requested to review the specification of the application. The utility of the claimed invention is expressed throughout the specification.

The claimed invention of the present application is not an intermediate compound merely for use in making a different end-product but, rather, it is the product which is used by a mass spectrometer for determining the molecular weight of a parent compound. The utility of the claimed composition of matter is clearly evident in that, now, scientists, researchers and others can make precise molecular weight determinations of large compounds using mass spectrometers of low nominal mass ranges. As a direct consequence of the present invention, the nominal range of a mass spectrometer is increased by a factor not less than the minimum number of charges which are carried by the multiply charged ions. For example, if, according to the present invention as disclosed, the minimum number of charge of one of the sequence of sub-populations of the new composition of matter is 6 charges, then the nominal range of the mass spectrometer is increased six fold. Thus, assuming for purposes of this example, that the nominal mass range of the mass analyzer was merely 5000 Daltons, the mass range is extended by using the new claimed composition of matter so as to be capable of a precise molecular weight determination for compounds of about 30,000 Daltons. It is evident that the nominal mass range of the mass spectrometer has been increased as a direct consequence of the high number of multiple charges on the ions. This new composition of matter, described in the present application, is the subject of the claims.

The claimed new composition of matter has properties that make it now possible to conveniently and accurately determine the molecular weight of parent molecular species from which the new composition of matter is formed. This ability to determine molecular weight and, indeed, the molecular weight itself that is determined directly from the claimed new composition of matter are extremely useful pieces of information. They have real market value. When Applicants first learned how to make the claimed composition of matter,

individuals and corporations were willing to pay for each accurate determination of the molecular weight of a single species. Now, as a consequence of the present invention, there are many investigators, researchers and laboratories throughout the world that are producing the claimed composition of matter to determine the molecular weight of the species from which the claimed compositions are produced.

At the Annual Meeting of the American Society of Mass Spectrometry in June of 1994, there were many published papers involving what has come to be commonly known as "Electro Spray Mass Spectrometry" or ESMS. Most of those papers related to the production of the claimed ion populations for the purpose of determining the molecular weight of the parent molecular species from which those claimed populations, the new composition of matter, were produced.

In summary, Applicants respectfully suggest that the claimed new composition of matter is not an "intermediate" product, used to make other compounds, without regard for the usefulness of the latter compounds but, rather, the claimed new composition of matter is an end product whose properties make it a useful and very valuable item of commerce.

A new chemical compound with a particular formula can be claimed and allowed as a new composition of matter if it has diverse properties that make it useful in the treatment or diagnosis, for example, of disease. That, of course, is one example of utility for a new compound. Applicants submit that the claimed ion populations are also, similarly, a new composition of matter whose properties make them useful. Useful, however, in a different manner but, still very useful and valuable. The claimed compositions are useful in determining the molecular weights of the compounds from which they are produced. Indeed, the claimed composition of matter is being increasingly produced and used by, for example, pharmaceutical companies because the information, a determination of molecular weight of the parent compound, plays an essential role in the development of new drugs and therapeutic agents. It is with the above that Applicants respectfully request that the Examiner reconsider his rejection of the claims. The Examiner's rejection of the application on grounds of lack of utility ought to be withdrawn.

To summarize, the claimed composition of matter is highly useful in the determination of molecular weight. The composition is not an intermediate product but, rather, the claimed

composition of matter is, itself, useful in determining molecular weight of the parent molecular species from which the multiply charged ions are produced. This is useful and disclosed in the specification.

The composition of matter as described in the patent application specification comprises a population of multiply charged ions which are generated from a distinct polyatomic molecular species. The polyatomic molecular species have been described in the specification as having "essentially the same molecular weight (except for isotopic differences)". The Examiner states that the polyatomic parent molecular species is a chemical compound. A distinct polyatomic parent molecular species could be described as a distinct chemical compound species and would have a distinct chemical formula. Molecules with a distinct chemical formula would have essentially the same molecular weight (except for isotopic differences). The composition of matter as described in the specification and claimed comprises a group of multiply charged ions which have a chemical formula different from the parent molecule chemical formula due to the addition of (or deletion of as can be the case with negative ions) adduct ions. The mass to charge value of the ion as measured by a mass spectrometer includes the adduct ion mass as expressed by the relationship $K_i = M/i + m_a$ given in the specification where K_i is the mass to charge ratio of a multiply charged ion and defines a particular sub-population. M is the molecular weight in atomic mass units (amu) of the distinct polyatomic molecular species, i is the integer number of charges and m_a is the average adduct ion molecular weight. In these terms, each of the distinct populations of ions as defined in the claims comprise a mixture of ions wherein each ion with the same number of adduct ion charges defines a sub-population of ions within the population.

This mixture of sub-populations of ions comprise the particular population of multiply charged ions that make possible the convenient and accurate determination of the molecular weight of the parent molecular species from which the population of ions is formed. This ability to use the composition of matter to obtain the value of the molecular weight of the parent molecular species is a useful piece of information that has a real commercial value. It is important to note that the composition of matter is in itself the end product which is created for a particular purpose of gaining molecular weight information about the parent molecular species from which the composition of matter was made. The molecular weight

measurement is an important and often key piece of information which is required in structural determination of molecules, reaction monitoring, sample purity determination and other facets of chemical analysis as well as giving specific information as to the presence and relative abundance of a compound type. A molecular weight measurement, in particular the appearance of a peak or series of related peaks in a mass spectrum, in itself yields a definitive piece of information. The resulting value of molecular weight, attained from the mass measurement, does not imply an answer to a question, it is itself a precise and definitive piece of information. As the specification describes, the population of multiply charged ions comprising a group of sub-populations can yield a specific measure of molecular weight. Hence the composition of matter is directly used to yield a specific and valuable piece of information.

The Examiner seems to have overlooked the most direct utility of the invention. The production of a mass spectrum from the claimed composition of matter can be used to determine the molecular weight of the compound being investigated. A significant portion of the patent specification is dedicated to describing this utility. The multiply charged ions, the claimed composition of matter, is a form of matter which allows for the acquisition of very useful information as a consequence of using the new matter in a mass spectrometer. Neither of the cases, Joly or Kirk, considers any other utility for a new form of matter except a chemical utility. In the present case, we have a set of highly charged ions which allow the measurement of molecular weight, which for a singly charged compound may be beyond the range of the mass spectrometer used to generate the spectrum. That is, if the molecule were not highly multiply charged then the mass spectrometer could not be used to determine its molecular weight. The claimed material allows for low mass range machines to be used for compounds well above the nominal mass range.

Utility of the claimed composition, as described in the specification, is summarized as follows:

1. Ions when produced and introduced into a mass spectrometer can be used to produce a mass spectrum from which the molecular weight of the compound can be determined.

2. The multiple charging of the claimed ions allows the determination of molecular weights for masses beyond the singly charged mass range of the mass spectrometer.

3. The plurality of sub-populations of charge states allows multiple measurements and averaging of the molecular weight within one spectrum, through methods described in the specification. This results in higher accuracy in mass measurement than can be achieved readily from a single ion peak measurement.

4. The multiplicity of charges may enhance the detector response in mass spectrometric measurements.

5. The total current carried by one species is greater when there is peak multiplicity than would be the case for a single peak containing the same total number of singly charged ions.

Based on the above, applicants submit that the rejection on the ground of lack of utility ought to be withdrawn.

Applicant has submitted a new set of claims. These new claims are fully supported by the specification and are believed to be patentably distinct over the known prior art. In the absence of an uncovering by the Examiner of more pertinent prior art, this application is believed to be in a condition of allowance. No new matter has been submitted in the newly submitted claims. Rather, the claims, as now submitted, are believed to more clearly define that which the Applicants claim as their invention.

Applicants submit herewith a reference, Determination of Non-Derivatized Peptides by Thermospray Liquid Chromatography/Mass Spectrometry, Pilosof, Kim, Dyckes and Vestal, Anal. Chem., Vol. 58, 1984, pp. 1236-40, which is related to the subject matter of the claimed invention. The claims of record, as presented, patentably define over the teaching of this reference. In brief summary, the reference relates to producing ions for analysis in a mass spectrometer by use of the Thermospray technique. Thermospray, to Applicant's knowledge, has not produced nor is it apparently capable of producing the composition of matter, as claimed. A brief discussion of thermospray in comparison to electrospray is contained in the original specification. See, for example, pages 4-5. More specifically, the

referenced publication contains a mass spectrum (Figure 4) with multiple charge of glucagon showing what the authors claims are +3 and +4 peaks. The publication does not anticipate nor render obvious the invention of the current patent application.

A Thermospray (TS) ion source was used to generate a mass spectrum of glucagon in Figure 4 of the reference. This Thermospray ion source (described in the patent application on pages 4-5) creates charged droplets through rapid evaporation of liquid as it flows directly into vacuum. The charging is a result of statistical fluctuations in the distribution of cations and anions as the liquid is nebulized. The claimed invention is created using an Electrospray ionization process. In contrast to Thermospray, Electrospray (ES) "can be considered a sort of mirror image of TS ... in that instead of producing charging by atomization it produces atomization by charging" (current patent application specification pp. 4-5). Electrospray produces charged droplets at approximately atmospheric pressure from which the multiply charged ions are produced. For species of large molecular weight, ES ionization produces multiply charged ions which have charge numbers "distributed between a minimum and maximum of charge states." Electrospray charged droplet production does not require the addition of heat as is necessary with Thermospray. Consequently, the ES process can generate ions from large thermally labile compounds without thermal degradation. The process of Electrospray as contrasted with Thermospray produces droplets with a much higher charge density and the charged droplets produced by ES have not required the addition of heat. Ion production from Electrospray droplets can be achieved for very large thermally liable compounds. The high degree of charging in Electrospray plays a significant role in the mechanism of producing ions with high degrees of multiple charging. The TS process has increasing difficulty in producing ions from molecules which have a molecular weight over 3000 amu or from very thermally labile or fragile molecules.

The cited article reports that no +3 or +4 peaks of glucagon could be achieved with TS when using a solution of pH 5.5. Only after lowering the solution pH to 1.85 (with the addition of 0.1 M trifluoroacetic acid) were the +3 and +4 peaks of glucagon produced by TS. The +3 and +4 peaks, as shown in Figure 4, are very broad (over 50 amu for the +3 peak) due to the need to reduce the quadrupole resolution to "increase the transfer efficiency of the quadrupole" and due to "the result of the presence of sodium and potassium adducts" (as

stated in article). Two nanomoles of glucagon were injected to achieve the TS spectrum in Figure 4. Thus, modifications to solution chemistry, detuning of the mass analyzer resolution and injection of large amounts of sample were required by TS to achieve detectable +3 and +4 peaks of glucagon. By contrast, a mass spectrum of glucagon is attached which was generated using Electrospray ionization. Two picomole/ul glucagon in a solution of 1:1 methanol:water (neutral pH) was infused into an Electrospray ion source. With less than 1/1000th of the sample consumed and a solution with a pH above 5.5, the Electrospray ion source produced a spectrum of +3 and +4 peaks at higher resolution, with less adduct peaks, greater signal to noise, and a peak width of approximately 0.5 amu at full width half maximum (FWHM). Electrospray can produce +3 and +4 peaks from glucagon run with solutions that the Thermospray technique fails to produce +3 and +4 peaks.


The authors of the cited article gave no indication or suggestion that Thermospray could be used to produce higher charge states than +4 nor that Thermospray will produce mass spectrum with multiply charged peaks from compounds of higher molecular weight than glucagon. Such extreme running conditions of solution chemistry pH, large sample amounts injected and mass spectrometer resolution detuning to produce a mass spectrum of glucagon with unresolved peaks over 50 mass units wide with the Thermospray technique has limited practical utility as an analytical tool. The article cited did not anticipate that compounds with higher molecular weights than glucagon would produce a multiply charged mass spectrum with the Thermospray technique or any technique. As the present specification states, the ability of Electrospray to produce highly multiply charged ions from compounds over a wide range of molecular weights was a major breakthrough in mass spectrometric analysis of high molecular weight molecules. Indeed the market place bears this out as Electrospray has become, over the last few years, the most widely used ion source for liquid chromatography/mass spectrometry (LC/MS) interfacing and on-line analysis while the use of Thermospray has diminished over the same time period. The ability of Electrospray to produce highly charged ions from high molecular mass compounds allowed very sensitive accurate mass determination in a simple and routine manner and by use of mass spectrometers of relative low nominal mass ranges.

In summary, the cited article which reports on using the Thermospray technique did not demonstrate nor anticipate the ability of Thermospray to produce ions with higher molecular weight or charge states higher than +4 from which a mass analysis could be performed. The ability of Electrospray, an atmospheric pressure ionization technique, to produce multiply charged ions with charge states greater than +4 from large thermally labile compounds that would be usable for determination of molecular weight of an unknown compound was not obvious to the authors of the cited paper. It was not obvious to others in the field either. Between 1984 when the cited article was published and 1988 when the present invention was disclosed at the 1988 ASMS conference (as is reported in the patent application's specification) Thermospray continued to exhibit limitations in its ability to ionize higher molecular weight or more thermally labile compounds with or without multiple charging.

Prompt and favorable action is earnestly solicited. In the event the Examiner believes that further informalities exist either in the specification or in the claim language, the undersigned respectfully requests that the Examiner telephone the attorney of record in an attempt to reach resolution on the informalities. Prompt and favorable action leading to issuance of the captioned application is believed warranted.

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